PATENT COOPERATION TREATY

05 JUL 2005

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or Agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR 03/02354	International filing date *(day/month/year)* 25.07.2003	Priority date *(day/month/year)* 26.07.2002
International Patent Classification (IPC) or national classification and IPC C07D487/04		
Applicant GREENPHARMA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets including this title page.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Instruction 607 of Administrative Instructions of the PCT).

   These annexes consist of a total of 27 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   IV ☒ Lack of unity of invention

   V ☒ Reasoned statement according to Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.02.2004	09.11.2004
Name and mailing address of the IPEA European Patent Office D-80298 Munich Tel. +49 89 2399 - 0, Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer: Boletti-Crèmers, K Telephone No. +49 89 2399-8541

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/FR 03/02354

I. Basis of the report

1. This report has been drawn up on the basis of the following elements *(the replacement sheets received by the receiving office in response to an invitation according to Article 14 are considered in the present report as "originally filed" and are not annexed to the report as they contain no amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-66 as originally filed

Claims, No.:

1-20 received on 25.10.2004 with the fax

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, nos.:

☐ the drawings, sheets:

5. ☐ This report has been written disregarding (some of) the amendments, which were considered as going beyond the description of the invention, as filed, as is indicated below (Rule 70.2(c)):

(All replacement sheets comprising amendments of this nature should be indicated in point 1 and attached to this report).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-2

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings (indicate particular elements below) or said claims Nos. 1 and 2 are so unclear that no meaningful opinion could be formed (specify):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 1, 2.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict the claims or pay additional fees.

3. This Authority found that, according to Rules 13.1, 13.2 and 13.3:

   ☐ the requirement of unity of invention is complied with.

   ☒ the requirement of unity of the invention is not satisfied, for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 30-20 for type (Ia) compositions.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Yes:	Claims	
	No:	Claims	3-20 for all types of compositions
Inventive Step	Yes:	Claims	3-20 for type (Ia) compositions
	No:	Claims	
Industrial Applicability	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

   see separate sheet

POINT III and clarity

Before dealing with the examinations of novelty and of lack of unity of the claims with respect to the contents of the documents cited below, the IPEA wishes to comment that it entirely approves of the ground which led the ISA to restrict the claims search to claims 3, 6, 7, 11 and 12, namely the **lack of foundation** of the claims which cover the desired protection in its entirety, that is to say mainly claims 1, 2, 4, 5 and 8, and the IPEA also wishes to further **and especially** add to this the **lack of clarity of claim 1** and also of all the claims which directly or indirectly refer to this claim.

In fact, claim 1 is provided with definitions of radicals which, even though they are clear per se, are accompanied with so many conditions (see 69 of claim 1, lines 8-29; see also lines 29-31 of page 68) and exclusions (*with the proviso*, etc.) that it is impossible to deduce therefrom with certainty the exact scope of the possibilities (implicit and explicit) and, sometimes, their real definitions.

In this context, since the exclusions of claim 1 involve definitions of compounds that are clearer than the definitions of the compounds which are supposed to exclude them, the IPEA will preferably concentrate the remainder of the opinion on the claims for which a search was carried out, and which, overall, concern compounds in relation with the exclusions in question, namely claims 3, 6, 7, 11 and 12 mentioned above.

POINT IV (lack of unity)

The IPEA is of the opinion that the application lacks unity, for reasons that are different from those mentioned by the ISA.
The application concerns, first and foremost, the production of medicinal products, that are useful in human or veterinary therapy, intended to increase the synthesis and/or the release of neurotrophic factors.

Starting from only documents (1)-(5) mentioned below, which all relate to the same type of therapeutic application or to a related therapeutic application, the problem that the present application proposes to solve is that of producing medicinal alternatives to that of documents (1)-(5), and the solutions proposed in claim 3, namely the compounds of type I_a and the compounds of type I_b, are not connected to one another by means of the same common inventive concept because they

require that 2 different prior arts are taken into consideration in order to examine the inventive step, namely, for the compounds of type I_a, document (3) and for the compounds of type (I_b), documents (1)-(5).

Consequently, the IPEA is of the opinion that the application according to claims 3-20 concerns 2 inventions, which are

the compounds of type (I_a) according to claims 3-20
the compounds of type (I_b), also according to claims 3-20.

The IPEA also wishes to point out that it may be that, during subsequent examination (Chap II or regional phase), the applicant may perhaps have to confront objections of nonunity other than the present one, depending on the impact of the prior art (or prior arts) on the application.

Insofar as, in its letter of 08.05.2004, the applicant chose the compounds of type I_a without restricting the application, i.e. by eliminating the compounds of type I_b, **the examination of the inventive step of the application according to chap II of the PCT will concern only the compounds of type I_a.**
The objection of lack of unity of the invention of 07.09.2004 is maintained.
However, when the application deals with the regional phase, the examination of lack of unity will be revisited, also taking into account the applicant's argument of 08.05.2004.

POINT V.

1. Novelty

The following documents, cited in the international search report, were considered to be relevant for the examination of the present application. The numbering thereof will be conserved for the remainder of the proceedings:

(1) WO-A-99/38868, cited in the application.
(2) WO-A-01/23388.
(3) Journal of Heterocyclic Chemistry, vol. 22, 1985, pages 601-634.

(4) WO-A-02/50079, cited in the application.

(5) FR-A-2 230 366.

(6) WO-A-02/072202 (point VI).

(7) J.O.C., (2002), 67(23), 8063-8071 (point VI), which relates to the thesis by Pierre Raboisson mentioned on page 8, lines 7-22 of the description.

1.1 (1), (2), (3), (4) and (5), which represent the prior art pursuant to chap II of the PCT, describe compounds of type I_b, which, "prima facie", all come **at least** (it should be noted that the compounds of (2) for which X:C also come under the wording of claim 1 of the application) under the wording of claim 3 and of all the claims which depend directly or indirectly thereon in as much as the compounds which are described therein are substituted in the 4-position of the pyrazolotriazine ring with a substituted or unsubstituted amine function, or else an OH, SH, ether or thioether function (see (3) for example).

1.2 The additional exclusion, at the end of claims 1 and 3, due to examples 10 (and not 6 as mentioned by the applicant), 29, 40, 41, 43, 65 and 78 of table I of (3) is not able to confer the novelty of the application with respect to the content of (3).

In fact, the compounds of examples 112-114 and 122 of (3) also come under the wording of claims 1 and 3 and do not seem to have been included in the exclusions as originally filed (see page 75, lines 19-23 of claim 1 as originally filed)

(3) (it should be noted that a large number of the compounds of (3), for which rings other than the pyrazolotriazine of claim 3 are mentioned, also come under the wording of claim 1 of the application.

1.3 Although (6), as filed on 03.06.2002 and published on 09.19.2002, and claiming a priority of 03.13.2001, is not of the prior art in the context of the proceedings pursuant to Chap II of the PCT, its content could affect the novelty of the application in the regional phase to come, since (4) also involves the preparation of compounds of type (I_b).

However, a thorough examination of this document, and the possible taking into account thereof, will depend on the examination of the validities of the

right of priority claimed by the application **and by (4)**, and will only be carried out when the application moves into the European regional phase, where there will perhaps also be reason to re-evaluate the inventive step of the application should it not benefit from a validly claimed right of priority.

1.4 Similarly, for (7), a thorough examination of this document will depend essentially on the validity of the rights of priority claimed by the application, and will only be carried out when the application moves into the European regional phase.
Prima facie (7) relates to the production of nucleosides of type I_b.

Although (7) in itself does not constitute prior art in the context of the PCT chap II, the thesis by Mr Raboisson, which was used as a support for the writing of document (7), could become prior art in the context of the regional phase, due to the fact that it (the thesis) was probably accessible to the public before the publication of (7). For this reason, the applicant will be requested to produce a copy of said thesis in the regional phase to come.

2. Inventive step

Due to the fact that the compounds of type I_a of the application have a pharmacological profile that is different from those mentioned in (3), the part of the application as claimed based on claim 3, and which relates to the compounds I_a, is declared inventive with respect to (3) in view of the applicant's argument of 10.19.2004.

3. Formal points

3.1 The claims lack clarity for the reasons mentioned in the introduction, and the applicant is requested to reformulate the claims in such a way that the clarity may be recognized in the regional phase to come, and **especially** in such a way that a thorough search with respect to the claims is possible in the regional phase.

3.2 (2), (3) and (5) should be mentioned and briefly discussed in the description when moving into the regional phase.